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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,263	RUSSELL ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,44-50,58,60-62 and 64-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,10-14,16,18-20,22,23,32-34,36,44-50,53,56,58,60-62,64-69,73,75,79 and 83-87.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,2,4,10-14,16,18-20,22,23,32-34,53,56,68,69,73,75,79 and 83-87.

DETAILED ACTION

1. Applicant's election with traverse of Group 3 in the reply filed on December 15, 2009 is acknowledged. The traversal is on the ground(s) that it would not be burdensome to examine all the indicated groups. This is not found persuasive because the instant application is a 371 application and restriction in 371 cases is based on unity of invention. Burden is not a factor in determining unity of invention. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression special technical features is defined in Rule 13.2 as meaning those technical features that define a contribution with each of the inventions, considered as a whole, makes over the prior art. In the instant application, the linking technical feature of polymorphic sites in the protein C gene does not constitute a contribution over the prior art. For example, Spek (Journal of Biological Chemistry 1995) teaches two mutations in the promoter region of the human protein c gene that cause thrombosis (see abstract). Further Spek teaches oligonucleotides specific for the detecting the polymorphisms. (see page 24217). Thus, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Additionally it is noted that Applicants have elected the following species for initial examination:

A. the Protein C sequence (SEQ ID NO: 1)

B. the SNP at position 4732 of the Protein C sequence (SEQ ID NO: 1)

C. systemic inflammatory response syndrome (SIRS) as the disease

D. activated protein C as the anti-inflammatory agent

2. Claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34, 36, 44-50, 53, 56, 58, 60-62, 64-69, 73, 75, 79, and 83-87 are currently pending.

Claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34, 53, 56, 68-69, 73, 75, 79, and 83-87 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 15, 2009.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because applicants are trying to claim foreign priority under 35 USC 119(a)-(d) to Application 2479968 filed in Canada on October 8, 2004. The foreign application is listed on the oath however it is listed under the section for applications claiming priority under 35 USC 119(e). As such a new oath is required.

Specification

4. The specification is objected to because all continuing data must be listed in the first paragraph of the specification if no Application Data Sheet has been filed.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlink is present on page 48.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 36, 44-49, and 66-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are broadly drawn to a method of treating an inflammatory condition in a subject in need thereof. The claims comprise selecting a subject having a

risk genotype in their protein C sequence and administering to said subject an anti-inflammatory agent or an anti-coagulant agent. The specification (page 34) defines a risk genotype as an allelic variant (genotype) at one or more polymorphic sites within the Protein C sequence that is indicative of a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. The claims encompass selecting a subject having any polymorphic variant at one or more polymorphic sites within the protein C gene that is associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

When the claims are analyzed in light of the specification, the instant invention encompasses selecting a subject (human or non human) having one or more of an enormous and wide variety of allelic variants in the protein C gene. Thus the claims encompass the selection of subjects having many different protein C nucleic acid sequences wherein the protein C nucleic acid sequences are correlated with a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of the protein C gene (SEQ ID No. 1) and discloses several polymorphic variations of SEQ ID NO: 1. Specifically the specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 is correlated with decreased survival and

increased multiple organ dysfunction. The specification further describes additional polymorphic variations that are in linkage disequilibrium with position 4732. Of the polymorphisms that are in linkage disequilibrium with position 4732 only one, namely at position 4800 (r^2 value of 0.85), was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not provide any characteristics that would allow one to identify any particular polymorphic variants of the disclosed sequence that are correlated with a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

Applicants' attention is directed to the decision in *In re Shokal,* 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, one of skill in the art cannot envision the detailed chemical structure of all of the nucleic acids encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation or use. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method comprising selecting a subject having a risk genotype in their protein C sequence that is associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

7. Claims 36, 44-50, 58, 60-62, and 64-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of treating SIRS in a human subject, the method comprising selecting a subject that is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO: 1 and administering to said subject activated protein C, does not reasonably provide enablement for a method of treating an inflammatory condition in a subject by selecting a subject having a risk genotype in their protein C sequence and administering to said subject an anti-inflammatory agent or an anti-coagulant agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention and the breadth of the claims

The claims are broadly drawn to a method of treating an inflammatory condition in a subject in need thereof. The claims comprise selecting a subject having a risk genotype in their protein C sequence and administering to said subject an anti-inflammatory agent or an anti-coagulant agent.

The specification (page 34) defines a risk genotype as an allelic variant (genotype) at one or more polymorphic sites within the Protein C sequence that is indicative of a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. As such the claims encompass selecting a subject having any polymorphic variant at one or more sites in the protein C gene that is associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. Only claims 50, 58, and 62 define polymorphic variant in the protein C gene that is associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

The claims encompass any type of inflammatory condition. Only claims 48 and 49 recite specific types of inflammatory conditions.

The claims encompass any type of subject, human and non human.

Finally the claims encompass any type of anti-inflammatory agent or anti coagulant agent. Only claims 66 and 67 recite specific agents.

The nature of the claims requires the selection of subjects having many different protein C nucleic acid sequences wherein the protein C nucleic acid sequences are correlated with a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome and administering to said subject an anti-inflammatory agent or an anti-coagulant agent.

Guidance in the Specification and Working Examples

Example 2 in the specification teaches an association between the C allele at position 4732 of SEQ ID NO: 1 and altered survival and organ dysfunction in critically ill adults with SIRS. Specifically the specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. The specification further discloses other polymorphic variations that are in linkage disequilibrium with position 4732. Of the polymorphisms that are in linkage disequilibrium with position 4732 only one, namely at position 4800 (r^2 value of 0.85) was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome.

Example 4 in the specification is directed to whether or not treatment with activated protein C (XIGRIS) can reduce organ dysfunction in subjects who have sepsis and who have an at risk genotype of protein C such as the C allele at position 4732. The 28 day survival rates for patients who were protein C 4732 CC/CT were compared to patients who were protein C 4732 TT with and without treatment of XIGRIS. The results indicated that XIGRIS treatment increases survival (compared to no treatment)

of patients who were protein C 4732 CT/CC (See Fig 7). Further the results indicated that XIGRIS treatment had virtually no effect on survival rate over 28 days in patients who were protein C 47322 TT.

Accordingly the specification is enabled for a method of treating SIRS in a human subject, the method comprising selecting a subject that is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO: 1 and administering to said subject activated protein C.

In the instant case the specification does not provide guidance on how to predictably associate any polymorphic variant at one or more positions of the protein C sequence with altered survival and organ dysfunction in critically ill adults with SIRS. The specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. Regarding the disclosed polymorphisms that are in linkage disequilibrium with position 4732 only one, namely at position 4800 (r^2 value of 0.85) was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome. However there is no disclosed correlation between the SNP at position 4800 and increased survival when treated with XIGRIS (activated protein C). Further it is noted that all of the findings in the specification are limited to patients with SIRS yet the claims encompass patients with any type of inflammatory condition. Further the claims encompass human and non human subjects but the teachings in the specification are limited to humans. Although the specification teaches that XIGRIS treatment increases

survival (compared to no treatment) of patients who were protein C 4732 CT/CC, the specification does not demonstrate that treatment with any other anti-inflammatory agent or anti-coagulant agent will also increase survival (compared to no treatment) of patients who were protein C 4732 CT/CC.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Given the large size of the protein C gene (over 10 kb), there are expected to be a numerous mutations in the protein C gene. However the specification does not teach a predictable means for distinguishing between variations that are correlated with altered survival and organ dysfunction in critically ill adults with SIRS and naturally occurring variations. Further the specification does not teach a predictable means for identifying additional variations in the protein C gene that are correlated with altered survival and organ dysfunction in critically ill adults with SIRS. The specification only teaches 2 variants in the protein C gene, namely at positions 4732 and 4800 of SEQ ID NO: 1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS.

Further it is noted that the specification teaches several variants that are in linkage disequilibrium with the polymorphism at position 4732. However it is highly unpredictable if a polymorphism in linkage disequilibrium with the polymorphism at position 4732 of SEQ ID NO: 1, 95%, 90%, 80%, 75% of the time will also be associated with altered survival and organ dysfunction in critically ill adults with SIRS. This unpredictability is highlighted by the teachings of Langdahl (Journal of Bone and Mineral Research 2000). Langdahl teaches that linkage disequilibrium between alleles is population dependent and there can be considerable variation between the frequencies at which alleles are inherited. For example the reference sites that while one group reported that a repeat polymorphism in the IL-1RN gene was in linkage disequilibrium with the IL-1B (+3§54) polymorphism, Langdahl et al were unable to show linkage between these polymorphisms. Additionally Wall (Nature Reviews Genetics (2003) volume 4, pages 587-597) teaches that linkage disequilibrium (LD) refers to the fact that particular alleles at nearby sites can co-occur on the same haplotype more often than is expected by chance (page 587, 1st column, 1st paragraph). Wall teaches that patterns of LD are known to be noisy and unpredictable as pairs of sites tens of kilo bases apart might be in complete LD, whereas nearby sites from the same region can be in weak LD (page 587, 2nd column, last paragraph). Wall teaches that population history, population size, and population structure lead to differences in LD (page 588, 1st column, top). Wall teaches, “Measuring LD across a region is not straightforward" (box 1, last paragraph, page 588). Wall teaches it is difficult to compare results from different LD studies directly because of the variation in

study design and methods of analyzing the data (page 591, 2nd column, 1st full paragraph). Wall teaches there are clear differences in LD between African's and non-Africans (page 593, 1st column). Thus Wall teaches that LD is not predictable. As such both Langdahl and Wall demonstrate the unpredictability in associating a polymorphism in linkage disequilibrium with the polymorphism at position 4732 of SEQ ID NO: 1 as a means for selecting a subject with SIRS having altered survival and organ dysfunction.

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. Knowledge that mutations in a gene occur in one organism (i.e. humans) does not allow one to conclude that this gene, and mutations in this gene will also occur in other organisms and will be associated with altered survival and organ dysfunction in patients with SIRS. Here it is noted that the specification does not teach homologues of the protein C gene in a representative number of different organisms. Thus it is unpredictable as to whether the protein C gene, and particularly the T4732C mutation, will be present in other organisms and will be associated with altered survival and organ dysfunction in subjects with SIRS.

It is also unpredictable as to whether the results obtained with SIRS can be extrapolated to other inflammatory conditions. The genus of inflammatory conditions is quite large and each condition has its own pathology and etiology. Again it is noted that the teachings in the specification are limited to an association between the T4732C mutation and altered survival and organ dysfunction in patients with SIRS. Given the differences in the causes and effect of each type of inflammatory disease, one can not extrapolate the results found in SIRS subjects to any type of inflammatory condition.

Additionally it is unpredictable as to whether the results obtained with activated protein C can be extrapolated to other of anti-inflammatory agents or anti-coagulant agents. The genus of anti-inflammatory agents and anti-coagulant agents is quite large. The teachings in the specification are limited to an association between the C allele at position 4732 of SEQ ID NO: 1 and an improved response to therapy with activated protein C. There are no examples in the specification in which SIRS patients were treated with other types of anti-inflammatory agents and anti-coagulant agents. In the absence of evidence to the contrary it is highly unpredictable how SIRS patients having at least one C allele at position 4732 of SEQ ID NO: 1 would respond to therapy with other drugs.

Quantity of Experimentation

The specification teaches 2 variants in the protein C gene, namely at positions 4732 and 4800 of SEQ I DNO: 1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS. To identify additional variants of the protein C gene which are associated with altered survival and organ dysfunction in critically ill adults with SIRS would require extensive experimentation. Even if the extensive experimentation was performed, there is no assurance that any other additional variants would be found. If additional variants were found that were associated with altered survival and organ dysfunction then even more experimentation would be required to determine if individuals having those variants showed an improved response to therapy with activated protein C. Such random, trial by error experimentation is considered to

be undue and highly unpredictable. The specification has provided only an invitation to experiment.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention in the full scope of the claims.

8. It is noted that the claims rejected below in sections 10 and 12-14 have been rejected under 35 USC 102 and 103 as anticipated by, or obvious in view of, the prior art and they have been rejected under 35 USC 112 1st paragraph as not fully described or enabled by the specification as originally filed. In the instant case, where the prior art does anticipate and render obvious particular embodiments of the broadly claimed methods, the prior art is not sufficient to provide an adequate written description of the breadth of the claims, nor is the prior art sufficient to enable the skilled artisan to practice the claimed method in the full scope of the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 36, 44-45, 48, and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Yan (Chest 2001) as evidenced by Reitsma (Nucleic Acids Research 1996).

Regarding Claim 36 Yan conducted a clinical trial to investigate whether protein C levels predict 30 day mortality rate, shock status, duration of ICU stay, and ventilator dependence in patients with sepsis. Seventy of the patients included in the trial had severe sepsis and failure in one or more organ. A total of 63 out of the 70 patients (90%) had acquired protein C deficiency. Yan found that presence and severity of acquired protein C deficiency was associated with poor clinical outcome, including lower survival rate, higher incidence of shock, and fewer ICR free and ventilator free days. Yan further teaches that the patients were either treated with ibuprofen or a placebo (abstract). As evidenced by Reitsma there are at least 160 different known mutations in the protein C gene that result in protein C deficiency (page 157, col 2). Thus Yan teaches selecting 63 subjects that have at least one mutation in their protein C gene that causes protein C deficiency and administering to the subject an anti-inflammatory agent such as ibuprofen.

Regarding Claim 44 Yan teaches that all patients enrolled in the study had an APACHE score calculated at study entry (page 916).

Regarding Claim 45 Yan teaches that all patients had to exhibit dysfunction of at least one of the following organ systems: cardiovascular, renal, ARDS/pulmonary, or CNS.

Regarding Claims 48 and 49 Yan teaches that the sepsis patients with a known or suspected site of serious infection had to meet all of the following criteria: core temperature, ≥ 38.3°C or < 35.5°C; heart rate, ≥ 90 beats/min in the absence of β-blocker treatment; and respiratory rate, ≥ 20 breaths/min (or minute ventilation, > 10 L/min if the patient requires mechanical ventilation). Here it is noted that the instant specification defines systemic inflammatory response syndrome as including both septic (i.e. sepsis or septic shock) and non-septic systemic inflammatory response (i.e. post operative). The specification teaches that " SIRS" is further defined according to ACCP (American College of Chest Physicians) guidelines as the presence of two or more of A) temperature >38ºC or <36ºC, B) heart rate >90 beats per minute, C) respiratory rate >20 breaths per minute, and D) white blood cell count >12,000 per mm^3 or <4,000 mm^3. Since the patients of Yan meet two or more of the criteria in the ACCP guidelines they are being interpreted as having SIRS.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12 Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan (Chest 2001) as evidenced by Reitsma (Nucleic Acids Research 1996) and in view of Grinnell (EP 0913156 Pub 1999)

Yan conducted a clinical trial to investigate whether protein C levels predict 30 day mortality rate, shock status, duration of ICU stay, and ventilator dependence in patients with sepsis. Seventy of the patients included in the trial had severe sepsis and failure in one or more organ. A total of 63 out of the 70 patients (90%) had acquired protein C deficiency. Yan found that presence and severity of acquired protein C deficiency was associated with poor clinical outcome, including lower survival rate, higher incidence of shock, and fewer ICR free and ventilator free days. Yan further teaches that the patients were either treated with ibuprofen or a placebo (abstract). As

evidenced by Reitsma there are at least 160 different known mutations in the protein C gene that result in protein C deficiency (page 157, col 2). Thus Yan teaches selecting 63 subjects that have at least one mutation in their protein C gene that causes protein C deficiency and administering to the subject an anti-inflammatory agent such as ibuprofen. Yan further teaches that all patients enrolled in the study had an APACHE score calculated at study entry (page 916).

Yan does not teach a method wherein an APACHE II score >25 is indicative of increased risk.

However Kruse that as APACHE II scores can be used to predict mortality. Kruse demonstrates that patients having an APACHE II score >25 are more likely to die than patients having APACHE II scores <25 (See Fig 2). Here 56 patients had sepsis. Thus Kruse teaches that APACHE II score >25 are indicative of increased risk of mortality.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Yan (as evidenced by Reitsma) by determining that subjects with an APACHE score > 25 are at increased risk of mortality. In the instant case it was well known in the art that patients having an APACHE II score >25 are more likely to die than patients having APACHE II scores <25 (See Fig 2 of Kruse). One of skill in the art would have been motivated to determine that subjects with an APACHE score > 25 are at increased risk because the APACHE II scoring method is highly predictive of outcome.

13. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan (Chest 2001) as evidenced by Reitsma (Nucleic Acids Research 1996) and in view of Wilkinson (The Journal of Pediatrics 1987)

Yan conducted a clinical trial to investigate whether protein C levels predict 30 day mortality rate, shock status, duration of ICU stay, and ventilator dependence in patients with sepsis. Seventy of the patients included in the trial had severe sepsis and failure in one or more organ. A total of 63 out of the 70 patients (90%) had acquired protein C deficiency. Yan found that presence and severity of acquired protein C deficiency was associated with poor clinical outcome, including lower survival rate, higher incidence of shock, and fewer ICR free and ventilator free days. Yan further teaches that the patients were either treated with ibuprofen or a placebo (abstract). As evidenced by Reitsma there are at least 160 different known mutations in the protein C gene that result in protein C deficiency (page 157, col 2). Thus Yan teaches selecting 63 subjects that have at least one mutation in their protein C gene that causes protein C deficiency and administering to the subject an anti-inflammatory agent such as ibuprofen. Yan further teaches that all patients had to exhibit dysfunction of at least one of the following organ systems: cardiovascular, renal, ARDS/pulmonary, or CNS.

Yan does not teach a method wherein two or more organ system failures are indicative of increased subject risk.

However Wilkinson teaches that patients were studied to determine the association of multiple organ system failure with mortality. The mortality rates for two, three, or four or more failed organ systems were 26%, 62%, and 88% respectively

(abstract). Thus Wilkinson teaches method wherein two or more organ system failures are indicative of increased subject risk.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Yan (as evidenced by Reitsma) by determining that subjects with two or more organ failures were at an increased risk of mortality. In the instant case it was well known in the art that there is a correlation between the number of failed organs and mortality. One of skill in the art would have been motivated to determine that subjects with two or more organ failures were at an increased risk of mortality because the number of organ failures can be predictive of mortality.

14. Claims 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan (Chest 2001) as evidenced by Reitsma (Nucleic Acids Research 1996) and in view of Grinnell (EP 0913156 Pub 1999).

Yan conducted a clinical trial to investigate whether protein C levels predict 30 day mortality rate, shock status, duration of ICU stay, and ventilator dependence in patients with sepsis. Seventy of the patients included in the trial had severe sepsis and failure in one or more organ. A total of 63 out of the 70 patients (90%) had acquired protein C deficiency. Yan found that presence and severity of acquired protein C deficiency was associated with poor clinical outcome, including lower survival rate, higher incidence of shock, and fewer ICR free and ventilator free days. Yan further teaches that the patients were either treated with ibuprofen or a placebo (abstract). As

evidenced by Reitsma there are at least 160 different known mutations in the protein C gene that result in protein C deficiency (page 157, col 2). Thus Yan teaches selecting 63 subjects that have at least one mutation in their protein C gene that causes protein C deficiency and administering to the subject an anti-inflammatory agent such as ibuprofen.

Yan (as evidenced by Reitsma) does not teach a method wherein the anti-inflammatory agent is activated protein C.

However Grinnell teaches a method for treating patients with sepsis associated with acquired protein C deficiency. The method comprises administering activated protein C (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Yan (as evidenced by Reitsma) by administering activated protein C as suggested by Grinnell. In the instant case activated protein C was well known in the art and routinely used for treating sepsis. One of skill in the art would have been motivated to Yan by administering activated protein C because Yan teaches that activated protein C may reverse the acquired protein C deficiency in patients with sepsis and improve outcome (page 921).

Conclusion

15. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571)

272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner
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/Stephen Kapushoc/
Primary Examiner, Art Unit 1634